Original Article

Impact of enhanced recovery after surgery protocols on postoperative morbidity and mortality in patients undergoing routine hepatectomy: review of the current evidence

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Background: Enhanced recovery protocols are widely used in many areas of general surgery but had a limited penetration in perioperative management of patients undergoing liver resection. Recently, multiple publications described application of enhanced recovery after surgery (ERAS) program to hepatectomy patients but their definitive role is not established or accepted by hepatobiliary surgeons.

Methods: A comprehensive literature review of published series in English language medical sources detailing ERAS program application for hepatectomy for the period of 2006–2016 is performed.

Results: ERAS protocols are feasible and safe. They reduce length of stay in patients undergoing routine hepatectomy without negative impact on morbidity and mortality. There is potential for reduction of Clavien grade I–II complications, while major and surgical complications are similar to traditional care management group.

Conclusions: Application of ERAS program to patient undergoing hepatectomy reduces length of hospital stay without affecting perioperative morbidity or mortality and may represent a new standard of care for patients undergoing routine liver resection.

Keywords: Enhanced recovery after surgery (ERAS); hepatectomy; review

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Introduction

Hepatectomy is essential part of multidisciplinary approach in treatment of primary and secondary liver malignancies. Despite significant improvements in perioperative management and surgical technique, 30-day morbidity and mortality are reported to be at 14–55% (1,2) and 0–11.9% (1,2) respectfully and are associated with prolonged hospital stay and resources utilization.

Enhanced recovery after surgery (ERAS) protocols have been pioneered by Kehlet and include multimodality approach to perioperative care to reduce length of stay and complications rate. It was since successfully accepted by many surgical subspecialties but only recently applied in hepato-bilio-pancreatic surgery. With current data suggesting potential benefit in decreasing length of stay and decreasing complications rate, we decided to analyze an impact ERAS protocols have on perioperative morbidity and mortality among published series.

Methods

All studies, published in English medical literature for the

Table 1 Key ERAS elements applied in perioperative care of patients with routine hepatectomy

Multimodality anesthesia and analgesia
Epidural anesthesia
Local/regional local anesthetics infusion/injection
Non-opioid analgesia
Optimized fluid therapy
Fluid restriction
Goal-directed fluid therapy
Physical therapy
Aggressive early mobilization
Promoting early GI function
Limited or no nasogastric suction tube use
Early oral intake
Laxatives
Epidural/local anesthesia
Surgical drains management
Avoidance or selective surgical drains use
Early drains removal
Minimally invasive surgery
Laparoscopic or laparoscopic-assisted surgery

last 10 years (January 1st, 2006 to January 1st, 2016) with key words "enhanced recovery protocol" or "fast-track protocol" and "hepatectomy" or "liver resection" including more than 20 patients aged older than 18 years old were identified in PubMed database. All studies used similar approach in perioperative management incorporating key ERAS elements presented in *Table 1*. Both randomized and non-randomized studies were included. All pertinent data, including type of cases, type of study, study endpoints ,number of patients, morbidity and mortality, type of complications (medical *vs.* surgical) and impact of ERAS program were extracted and analyzed. Difference in morbidity and mortality, when available, was presented as statistically significant if p value was below 0.05.

Results

Fifteen studies were identified (3-17). All studies excluded patients with complex biliary or vascular reconstructions. Overall, nine studies were prospective, three were randomized control trials, two were retrospective studies and one observation study were found. Number of enrolled patients ranged from 26 to 304. Study endpoints varied and included feasibility, length of stay and perioperative morbidity, completion of fast-track/ERAS protocol and functional recovery. One study was examining effect of laxatives on GI recovery (6) and one study compared effects of intrathecal analgesia versus epidural analgesia (5). Two studies included only patients undergoing laparoscopic hepatectomy (4,8), four analyzed both laparoscopic and open procedures (4-17) while one study looked only on patients having major open hepatectomy (13). Remaining eight reports included only patients undergoing open hepatectomy (3,5-7,10-12,14). Overall characteristics of all studies are summarized in *Table 2*.

ERAS protocol impact on length of stay

Out of all studies, ten demonstrated statistically significant reduction of hospital stay (all three randomized studies, six prospective studies and one retrospective study). Study reported by Schultz (9) was excluded from analysis since it had no control group and studies by Hendry (6) and Koea (5) were excluded since both arms were managed according to similar ERAS protocol and primary endpoints were effects of laxatives on GI recovery and intrathecal *vs.* epidural anesthesia. Study by Connor (10) was reporting gradual introduction of ERAS elements over period of 6 years and was included in final analysis. After excluding abovementioned studies, seven remained studies demonstrated reduced length of stay by median of 2 days (range, 1.1–3 days).

Four published series reported no impact of eras program on length of stay (three prospective, one observational and one retrospective study). Studies of Stoot *et al.* (4) and Sánchez-Pérez *et al.* (8) were reporting ERAS protocol management of patient undergoing minor laparoscopic hepatectomy, while study of Dunne *et al.* (14) was comparing length of stay in early versus late ERAS management cohort. Dasari *et al.* (15) reported no difference in median length of stay in his report of 184 patients undergoing both open and laparoscopic hepatectomies. Takamoto *et al.* (13) reported completion of ERAS protocol goals and was not geared towards analyzing difference in length of stay.

ERAS protocol impact on postoperative complications and readmission rate.

Out of total 15 studies, 5 were excluded. Studies by Takamoto *et al.* (13) and Schultz *et al.* (9) did not have

Table 2 Summary of published series of ERAS programs in routine hepatectomy

Author	Year	Type of cases	Type of study	Number of patients	Study endpoints	Length of stay difference, days	30-day morbidity/ readmission, %	30-day mortality
van Dam (3)	2008	Open	Prospective	161 (61 ERAS)	Length of stay, mortality and morbidity	S (6 *vs.* 8)	NS (41% *vs.* 31%)/NS (13 *vs.* 10%)	NS (0% *vs.* 2%)
Stoot (4)	2008	Laparoscopic only	Prospective	26 (23 ERAS)	Length of stay, morbidity and mortality	NS (5 *vs.* 7)	NS (15% *vs.* 15%)/not described	NS (0%)
Koea (5)	2009	Open	Prospective	100 ERAS	Effect of intrathecal vs. epidural anesthesia on and readmission	S (4.7 *vs.* 6.8)	NS (19%)/NS	NS (0%)
Hendry (6)	2010	Open	RCT	68	Effect of laxatives and nutritional supplements in context of ERAS protocol	Laxatives significantly decrease time to flatus and length of stay	25%/7%	3%
Lin (7)	2011	Open	Prospective	117 (56 ERAS)	Length of stay, morbidity and mortality	S (7 *vs.* 11), decrease charges	NS (46% *vs.* 43%)/NS (3.3% *vs.* 7.1%)	NS (1.6% *vs.* 1.8%)
Sánchez-Pérez (8)	2012	Laparoscopic only (28 actual minor resections)	Observational	43 (26 ERAS)	Length of stay, morbidity and mortality	NS LOS (2 *vs.* 3)	NS (12% *vs.* 12%)/NS (5.8% *vs.* 3.8%)	NS (0%)
Schultz (9)	2012	Open + laparoscopic	Prospective, no control group	100 (all ERAS)	Length of stay, morbidity and mortality	Two days length of stay after laparoscopic and 5–6 days after open hepatectomy	25%/6%	NS (0%)
Connor (10)	2012	Open	Retrospective	120 (all ERAS)	Length of stay, morbidity and mortality	S (3 *vs.* 6)	26.6%/11.7%	1.6%
Jones (11)	2013	Open	RCT	91 (46 ERAS)	Length of stay, morbidity and mortality, medical fit to discharge	S (4 *vs.* 7)	NS (17% *vs.* 31%)/NS	NS (2% both)
Ni (12)	2013	Open	RCT	160 (80 ERAS)	Short term outcomes	S (6.9 *vs.* 8)	S (30% *vs.* 46%)/not reported	NS (0%)
Takamoto (13)	2014	Open, major hepatectomy only	Prospective	165 (all ERAS)	Completion of ERAS, not length of stay	82% successfully accomplished ERP goals by POD6	Not reported	Not reported

Table 2 *(continued)*

Table 2 *(continued)*

Author	Year	Type of cases	Type of study	Number of patients	Study endpoints	Length of stay difference, days	30-day morbidity/ readmission, %	30-day mortality
Dunne (14)	2014	Open	Retrospective, no control group, earlier *vs.* late ERAS experience	304 (all ERAS)	Feasibility study, length of stay, morbidity and mortality	NS LOS 6 days; decrease in >10-day stay	NS (38% *vs.* 38%)/not reported	NS (0.3% overall)
Dasari (15)	2015	Open + laparoscopic	Prospective	184 (94 ERAS)	length of stay, morbidity and mortality	NS, LOS 5 days	NS (34.4% *vs.* 32.9%)/ NS (12.9% *vs.* 9.8%)	NS (1% *vs.* 1%)-90 days mortality
Savikko (16)	2015	Open + laparoscopic	Prospective *vs.* historical control	134 (all ERAS)	Feasibility study, length of stay, morbidity and mortality	S (4 *vs.* 6)	S (37.3% *vs.* 71%)/NS (3% *vs.* 2%)	NS (0%)
Day (17)	2015	Open + laparoscopic	Prospective	75	Functional r length of stay, morbidity and mortality recovery	S (4.8 *vs.* 6.1)	S (37% *vs.* 61%) major comps/NS (9% *vs.* 12%)	NS (0 %)

control group and studies by Dunne (14), Hendry (6) and Koea (5) all compared patients treated with similar ERAS protocols. Of reminding ten studies, six were prospective, one retrospective, one observational and two randomized control studies. Majorities of studies have shown similar overall complication rate with decreased rate of either medical complications or grade I–II complications [Jones (11), Ni (12), Day (17)]. Dasari *et al.* (15) reported decrease in grade III–V (severe complications) with no impact on readmission rates. Readmission rate was similar in all studies with Connor *et al.* (10) noting trend in increased readmission rate towards later ERAS cohort which paralleled increase in postoperative complications.

ERAS protocol impact on postoperative mortality

Out of all 15 studies, study by Takamoto *et al.* did not report any mortality data and was excluded. Among remaining 14 studies, there was no statistically significant difference in perioperative mortality (range, 0–2%) (3-17).

Discussion

Based on available reports, implementation of ERAS program for patients undergoing routine hepatectomy reduces length of hospital stay, medical complications without negative impact on postoperative readmission or mortality. Reduction in length of stay was almost uniform finding, excluding studies concentrating on laparoscopic minor hepatectomies (4,8) where ERAS is unlikely to reduce it. Despite Dunne (14) reporting similar length of stay, that study was indeed a comparison of early versus late cohort of patients treated with the same protocol and there was reduction in number of patients staying more than 10 days. Dasari *et al.* (15) reported similar findings, however pre-ERAS and post-ERAS cohorts are difficult to compare since author unit already practiced some fast-track elements in their perioperative care before introduction of standardized protocol. Overall morbidity seems not to be affected by ERAS management, with some studies demonstrating decrease in medical and low-grade Clavien grade I–II complications. The only study reporting decrease in major complications (grade III–V) is by Dasari *et al.* (15), which appears to be mostly secondary to higher rate of intra-abdominal collections. There are no details given on a nature of intra-abdominal collections but in reviewing both pre-ERAS and ERAS cohorts, there is increased number of extended resections, open hepatectomy, hepatocellular

carcinoma and cirrhosis in pre-ERAS group which can potentially contribute to observed difference. Readmissions and mortality rates are similar in most of the studies. Connor *et al.* (10) reported increase in readmission rates with parallel decrease of length of stay under ERAS protocol below 4 days while overall complication rate was unaffected. That indicates that some postoperative complications specific to hepatectomy (intraabdominal collections/abscesses/bile leak) may present outside the typical length of stay of the patients managed by ERAS protocol. In the same study, development of complication, total amount of IV fluids given and performance of biliodigestive anastomosis were all associated with increased LOS.

While reporting positive impact on perioperative evolution of patient undergoing hepatectomy, there are significant drawbacks in many of analyzed studies, ranging from lack of control group and comparison to historical control to retrospective or observational character. Many centers had some elements of fast-track management before implementing standardized ERAS protocol and protocol itself varied between different studies. Adherence to ERAS protocol was not reported in majority of studies or was not tracked at all. Finally, some studies excluded certain patients, like those undergoing laparoscopic procedure (11) or bile duct resection (3,7,12), while others included only laparoscopic cases [48] or mixture of open and laparoscopic cases.

Conclusions

Perioperative ERAS management of the patients undergoing hepatectomy is safe. Hospital length of stay is reduced without adverse impact on postoperative complication rate and mortality. There is a potential for reduced medical or low grade (Clavien I–II) complications while surgical complications are unchanged. Further insight into adherence to ERAS protocol and comparison of similar type of cases/operative procedures is needed to implement ERAS protocol as a standard of care for patients after liver resections.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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